# JAC-Antimicrobial Resistance

# The appropriateness of empirical antibiotic therapy in the management of symptomatic urinary tract infection patients—a cross-sectional study in Nairobi County, Kenya

Hellen A. Onyango () <sup>1,2,3</sup>\*, Derek J. Sloan<sup>1</sup>, Katherine Keenan () <sup>2</sup>, Mike Kesby<sup>2</sup>, Caroline Ngugi<sup>3</sup>, Humphrey Gitonga<sup>4</sup> and Robert Hammond<sup>1</sup>

<sup>1</sup>School of Medicine, University of St Andrews, Scotland, UK; <sup>2</sup>School of Geography and Sustainable Development, University of St Andrews, Scotland, UK; <sup>3</sup>College of Health Sciences, Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya; <sup>4</sup>Centre for Microbiology Research, Kenya Medical Research Institute, Nairobi, Kenya

\*Corresponding author. E-mails: hao1@st-andrews.ac.uk, helenonyango@jkuat.ac.ke  $\&@Jb_Atwech; @kkeenanstA$ 

#### Received 24 May 2024; accepted 5 July 2024

**Background:** In low- and middle-income countries, symptomatic urinary tract infection (UTI) patients are often prescribed antibiotics without microbiological confirmation. UTIs caused by antibiotic-resistant bacteria are increasingly common, and this heightens the risk of empirical treatment failure. This study evaluates the appropriateness of empirical antibiotic therapy to UTI patients in Nairobi County, Kenya.

**Methods:** A hospital-based, cross-sectional study was conducted in Nairobi County, Kenya, amongst symptomatic adult and child patients. UTI was defined as a monoculture growth with colony counts of  $\geq 10^4$  cfu/mL. Antimicrobial susceptibility testing was performed by the Kirby–Bauer disc diffusion method. Empirical therapy was considered appropriate if the pathogen isolated was susceptible to the prescribed antibiotic and inappropriate if the pathogen was resistant to the prescribed antibiotic.

**Results:** A total of 552 participants were enrolled with a median age of 29 years (interquartile range: 24–36). The majority were female, 398 (72%). Of the 552, 274 (50%) received empirical antibiotic therapy, and 95/274 (35%) were confirmed to have UTI by culture. The antibiotics most frequently prescribed were fluoroquinolones [ciprofloxacin in 80 (30%) and levofloxacin 43 (16%)], amoxicillin–clavulanic acid in 48 (18%) and nitrofurantoin in 32 (12%). Amongst the 95 patients with bacteriological confirmation of UTI, 50 (53%) received appropriate empirical antibiotic therapy, whilst for 38 (40%) participants, the therapy was inappropriate.

**Conclusions:** The complexity of appropriate empirical treatment for UTIs is compounded by high levels of resistance in UTI pathogens. Antimicrobial resistance surveillance strategies that could help in designing appropriate empirical regimens in resource constrained settings should be adopted for optimal empiric therapy.

# Introduction

Antimicrobial resistance (AMR) is the ability of microorganisms to circumvent the toxic action of antimicrobial substances that otherwise would kill or inhibit them.<sup>1</sup> The prevalence of resistance in common disease-causing bacteria has increased globally, both in healthcare and in community settings.<sup>2</sup> Consequently, the WHO has now listed AMR as an emerging public health threat believed to account for over 700 000 deaths per year.<sup>3</sup> The burden of AMR is estimated to be highest in the low- and middle-income countries (LMICs), particularly in Africa,<sup>4</sup> where morbidity and mortality from infectious diseases are high and health facilities less well-resourced than those in high-income regions.<sup>5,6</sup> Large regional, interdisciplinary studies, including the Holistic Approach to Unravel Antimicrobial Resistance in East Africa (HATUA) project which was run across Kenya, Uganda and Tanzania, have reported multiple drivers of AMR. Relevant factors ranged from inappropriate antibiotic prescriptions to widespread non-prescription-based dispensing of antimicrobials for self-medication, antibiotic use in animals and environmental factors such as sanitation, as well as social-economic and structural drivers including the cost of seeking healthcare.<sup>7-9</sup> In hospital settings, factors such as inadequate diagnostic capabilities, poor antibiotic stewardship practices, poor adherence to treatment guidelines and lack of AMR surveillance have been associated with resistance.<sup>6,10</sup>

© The Author(s) 2024. Published by Oxford University Press on behalf of British Society for Antimicrobial Chemotherapy. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/ by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

Urinary tract infections (UTIs) are amongst the most common community-acquired bacterial infections and are the second most frequent clinical indication for antibiotic use<sup>11</sup> after respiratory infections.<sup>12</sup> Patients with suspected UTI are often initiated on antibiotic treatment before culture results are available. However, in some cases, approximately 40% of the bacteria that cause UTI are resistant to the antimicrobials prescribed.<sup>13</sup> In the recent past, the prevalence of multi-drug-resistant bacteria associated with UTI has increased,<sup>14</sup> making selection of therapy for community-acquired UTI complex. Guidelines for uncomplicated UTI treatment recommend customization of therapy based on local practice, circulating resistant organisms, drug availability and price.<sup>15</sup> In Nairobi County, Kenya, where this study was undertaken, nitrofurantoin 100 mg, amoxicillin-clavulanic acid 625 mg and amikacin 15-30 mg/kg are the recommended empirical antimicrobial therapy for community-acquired UTIs.<sup>16</sup> For recurrent infections, the guideline recommends that empirical therapy be guided by previous culture results pending urine culture and sensitivity results. Once available, therapy is tailored to prescribe the most narrow spectrum efficacious antibiotic wherever possible.<sup>16</sup>

The selection of empirical therapy for UTI management is dependent on the knowledge of circulating pathogens and their AMR patterns.<sup>17</sup> Of concern, therefore, is the lack of susceptibility data for community-acquired UTIs in many LMICs, including Kenya. This is mostly due to the challenges with culture and susceptibility testing, some of which include infrastructural constraints, limited funding, prolonged turnaround times (TATs) and lack of skilled personnel.<sup>4,18</sup> There is relatively limited information on the appropriateness of empirical antibiotic therapy in the management of community-acquired UTIs in LMICs. This study seeks to address the paucity of microbiological information on management of microbiologically confirmed UTI in symptomatic patients and evaluates the appropriateness of empirical UTI treatment based on culture and susceptibility results.

# Materials and methods

## Study design

A hospital-based cross-sectional study design was employed to recruit adult and child patients with UTI-like symptoms between July 2022 and April 2023.

## Study setting

The participants were recruited from Mama Lucy Kibaki Hospital (MLKH) and Mbagathi County Hospital (MCH) located within Nairobi County, as shown in Figure 1. The Kenyan healthcare system is structured in a hierarchical manner consisting of six levels I–VI in ascending order. MLKH and MCH are Level V public referral hospitals. MCH and MLKH serve a large catchment area comprising both the middle and low socio-economic groups. The two hospitals were selected as there was limited information on the resistance profiles of circulating uropathogens and UTI patients are often treated empirically without culture confirmation.

## Participant recruitment and sample collection

A resident clinician identified adult ( $\geq$ 18 years) and child (5–17 years) outpatients presenting with one or more symptoms suggestive of UTI or for other causes that made the clinician to believe they might also have a UTI. The symptoms included lower abdominal pain, dysuria, strong persistent urge to urinate, haematuria, frequent micturition and/or unexplained fever ( $\geq$ 38°C),

persistent irritability and suprapubic pain/tenderness to palpation in children. In addition to meeting the criteria of a presumptive UTI case, the participants had to meet the following criteria: report living within a 50 km radius from the hospital facility, have a mobile telephone number and be able to speak/understand/write either English or Kiswahili. The study objectives were explained, and patients willing to participate were taken through informed consent document in their preferred language. Consent was obtained from adult patients ( $\geq$ 18 years). Assent and consent were obtained for participants aged 13–17 years. Parents/quardians of participants aged <13 years consented on their behalf. Consenting participants signed and dated the consent forms. Participants/guardians who were not able to sign marked the consent with a thumb print. Consenting participants were issued with a unique identifiable number which linked their bar-coded consent form, demographic data guestionnaire, and urine sample collection container. Self-collected midstream urine on a 20 mL sterile plain screw-capped universal bottle was obtained from each patient after guidance on the collection procedure. Parents/guardians were guided on how to collect midstream urine from their children. The samples were stored in a cool box (4°C) and transported to the Kenya Medical Research Institute (KEMRI) laboratory for processing within 2 h.

# Data collection

A questionnaire was used to collect self-reported demographic information (age and gender) and previous antimicrobial use. Data regarding empirical antibiotic treatment were obtained from prescriptions administered to the patients during the hospital visit. All data were captured electronically into an epicollect database (https://five.epicollect.net is a free open-source data collection tool) and later linked to the laboratory urine culture results.

# Microbiological tests

#### Urine culture

Using a standard sterile loop, an aliquot (10 µL) of urine was plated directly on cystine lactose electrolyte deficient (CLED) agar, blood agar (BA) and MacConkey agar (Oxoid, Basingstoke, UK) and incubated aerobically at 35°C-37°C for 24 hours. After an overnight incubation, quantification of colony-forming units (cfus) was done by counting the number of colonies on a plate and multiplying by the dilution factor, as previously described by Miles *et al.*<sup>19</sup> Pure bacterial growth yielding colony counts of  $\geq$ 10000 (10<sup>4</sup>) cfu/mL was interpreted as a confirmed UTI case. A mixed culture (with more than one colony type) or growth of <10000 (10<sup>4</sup>) cfu/mL was non-confirmatory for UTI.

The organisms were identified to the species level using colonial morphological characteristics on CLED, BA, MacConkey agar (Oxoid, Basingstoke, UK), Gram stain (Sigma-Aldrich, USA) and standard biochemical tests. Sulphide indole motility test, methyl red, oxidase, urease, triple sugar iron and citrate utilization were used to identify Gram-negative organisms.<sup>20</sup> Coagulase, catalase and haemolytic patterns on BA were used to confirm the presence of Gram-positive bacteria. Where necessary, the analytical profile index (20E) test was used to confirm the identity of strains following the manufacturer's guidelines (bioMerieux, Charbonnieres, Les Bains, France).

#### Antimicrobial susceptibility test

Antimicrobial susceptibility testing (AST) was performed according to the Kirby-Bauer disc diffusion method.<sup>21</sup> The panel of antibiotic discs (Oxoid, Basingstoke, UK) tested included first line, amoxicillin–clavulanic acid (20/10  $\mu$ g), nitrofurantoin (300  $\mu$ g) and sulfamethoxazole/trimethoprim (23.75/1.25  $\mu$ g), and second line, ciprofloxacin (5  $\mu$ g) antibiotics used in the treatment of UTI as per local practice.<sup>16</sup> Other antibiotics included in the panel were ceftazidime (30  $\mu$ g), ceftriaxone (30  $\mu$ g), cefepime (30  $\mu$ g), cefoxitin (30  $\mu$ g), gentamycin (10  $\mu$ g), cefuroxime (30  $\mu$ g), erythromycin (15  $\mu$ g) and linezolid (30  $\mu$ g). Susceptibility or resistance to the tested antibiotics was determined using the zone diameter interpretative criteria (breakpoints) according to the CLSI guidelines.<sup>22</sup> Isolates that showed intermediate resistance to a given antibiotic were interpreted as resistant to that antibiotic. *Escherichia coli* (ATCC 25922) and *Staphylococcus aureus* (ATCC



Figure 1. Location of study sites, MLKH and MCH within Nairobi County, Kenya.

25923) were used as quality control organisms to validate antibiotic disc potency and quality of the test media.

#### Evaluation of the appropriateness of empirical treatment

Appropriateness of empiric treatment was assessed by evaluating the treatment prescribed during the initial hospital visit with the subsequent laboratory urine culture and susceptibility results. The hospital visit during which the patient was recruited, and urine sample obtained, was defined as the initial visit. Empirical treatment was taken as any antibiotic treatment prescribed to the patient during the initial visit prior to urine culture results. Appropriateness was assessed on an individual patient basis for those patients whose urine specimen yielded significant bacterial growth for UTI ( $\geq 10^4$  cfu/mL). Appropriate empirical antibiotic therapy (AEAT) was considered if a UTI was confirmed on urine culture and the antibiotics prescribed were effective in inhibiting growth of the isolated pathogen in vitro.<sup>23</sup> Inappropriate empirical antibiotic therapy (IEAT) was defined as UTI confirmed on laboratory culture, but with an isolated pathogen which was resistant to the antibiotic prescribed in vitro.<sup>23</sup> AEAT was expressed as the percentage of patients with a culture-positive urine specimen and isolated pathogen tested as sensitive to the antibiotic prescribed. Conversely, IAET was expressed as the percentage of patients with a culture-positive urine specimen who had an empiric prescription for which the isolated pathogen was tested as resistant.

## Statistical analysis

Data were downloaded from epicollect into Microsoft Excel (Microsoft Corp, Redmond, Washington, USA) and were analysed using STATA 16

(StataCorp. 2019. Stata 183 Statistical Software: Release 16. College Station, TX: StataCorp LLC). The questionnaire data were linked to urinalysis, empirical prescription and AST data using anonymous patient identifiers. Baseline characteristics of the study population were reported as median [interquartile range (IQR)] for age or as counts and percentages for categorical data. Differences between categorical variables were compared using the  $\chi^2$  test or Fisher's exact test where applicable. Statistical significance was considered at probability value of <0.05.

## Ethical approval

This study received approval from the University of St. Andrews Teaching and Research Ethics Committee, UK (approval no. MD15749); Jomo Kenyatta University of Agriculture and Technology Institutional Ethics Review Board, Kenya (approval no. JKU/IERC/02316/0166); and National Commission for Science Technology and Innovation, Kenya (approval no. P/21/12520). Nairobi Metropolitan Services, MLKH and MDH provided approvals for the access to the study sites. Informed consent was obtained from each participant included in the study.

# Results

## Characteristics of the study participants

Participants' characteristics are shown in Table 1. Five hundred and fifty-two were enrolled. The majority were adults, 494 (89.4%), and females accounted for 398 (72%). The most

Table 1.	Basic	demographic	characteristics	of	participants
					P P

Variable	Response	UTI (+)* n (%)	UTI (–)* n (%)
Average		124 (22.5)	428 (77.5)
Gender	Male	32 (26)	122 (29)
	Female	92 (74)	306 (71)
Age	5-10	9 (7.2)	21 (5)
-	11-20	12 (9.6)	37 (8.6)
	21-30	56 (45)	183 (43)
	31-40	25 (20)	103 (24)
	41-50	12 (9.6)	54 (13)
	>50	10 (8)	30 (7)
	No medication	76 (61)	240 (56)
Medication taken in two weeks prior to	Yes—antibiotics Yes—other	37 (30)	131 (31)
recruitment	medications	11 (8.8)	57 (13)

Demographic and clinical characteristics of study participants.

UTI (+)\*, culture-confirmed UTI positive; UTI (–)\*, culture-confirmed UTI negative.

frequent age bracket was 21–30 with a median age of 29 years (IQR: 24–36). Amongst the 552 enrolled patients, 236 (43%) had taken medication 2 weeks prior to enrolment, 168 (71%) of these had taken antibiotics, whilst 68 (29%) had taken medications other than antibiotics.

## Proportion of microbiologically confirmed UTI

The overall proportion of culture-confirmed UTI amongst the studied population was 22.5% (124/552), being significantly higher in females than males (Table 1). Of these, 274 (49.6%) received empirically prescribed antibiotic treatment, and 242 (43.8%) did not receive any antibiotic treatment, whilst for 36 (6.5%), it was not known whether they received an antibiotic or not (participants could not be reached by phone or failed to come back to the hospital for the laboratory results). Amongst the 274 that received empirical antibiotic therapy, urine culture-confirmed UTI in 95 (35%). Of the 242 that did not receive therapy, 27 (11.1%) had UTI confirmed. Amongst those whose therapy status was not known, two (5.5%) had confirmed UTI. There was a significant difference in UTI detection between those who received empirical therapy and those who did not (P value of <0.05).

## **Microbiological characteristics**

A total of 124 bacterial isolates were characterized from the 552 urine samples analysed, 97 (78%) of which were Gram-negative. The predominant uropathogen was *E. coli*, 64 (52%), followed by *Klebsiella* spp., 21 (17%); *S. aureus*, 14 (11.3%); coagulase-negative staphylococci (CoNS), 7 (5.6%); *Enterococcus faecalis*, 6 (4.8%), *Proteus* spp., 7 (5.6%); *Acinetobacter baumannii*, 1 (0.8%); *Pseudomonas aeruginosa*, 2 (1.6); and *Citrobacter koseri*, 2 (1.6%).

## AMR patterns

AMR profiles of the 124 isolated UTI pathogens are shown in Table 2. For Gram-negative organisms, resistance towards

common UTI treatments— $\beta$ -lactams, fluoroquinolones and aminoglycosides—ranged from 24% to 57%. Within the bacterial groups, *E. coli*, the predominant uropathogen, showed high resistance to sulfamethoxazole/trimethoprim at 77%, ciprofloxacin at 61%, amoxicillin–clavulanic acid at 47% and ceftriaxone at 52%, whilst nitrofurantoin was the most effective agent for *E. coli*. The overall resistance of Gram-positive bacteria was 52% for sulfamethoxazole/ trimethoprim, 67% for ciprofloxacin and 26% for amoxicillin– clavulanic acid. Nitrofurantoin and linezolid were the most effective agents against Gram-positive isolates.

# Empirical antimicrobial prescribing

There were 15 antibiotics and antibiotic combinations prescribed empirically. Most of the patients 244 (89.0%) received one antibiotic and 28 (10.2%) received 2 antibiotics, whilst 2 (0.7%) received 3 antibiotics (Figure 2). Antimicrobial treatment was prescribed to 49.6% of all patients, with a first-line empirical treatment recommended in national guidelines utilized in 29.6% of cases. The most frequently prescribed antibiotics were ciprofloxacin (30.3%), amoxicillin–clavulanic acid (17.5%), levofloxacin (15.7%), nitrofurantoin (11.6%) and cefuroxime (10.6%), whilst the least prescribed were sulfamethoxazole/trimethoprim (1.1%) and cefepime (0.4%). Ceftriaxone/ciprofloxacin and cefixime/azithromycin were the most prescribed combination therapies at 4.7% and 3.2%, respectively.

# Appropriateness of empirical antibiotic treatment (AEAT)

Of the 95 patients with bacteriological confirmation of UTI, the antimicrobial susceptibility results were compared with the empirical therapy prescribed. The most prescribed antibiotics empirically were found to be inappropriate as follows: ciprofloxacin was prescribed 27 times, but in 11 cases (41%), the isolated organisms were resistant; for amoxicillin–clavulanic acid, in 12 (40%) out of the 30 prescriptions, organisms were resistant; for nitrofurantoin, 4 (27%) of the 15 prescriptions proved to be inappropriate, and finally, cefuroxime was prescribed 7 times, but 6 (88%) cases were inappropriate. Overall, most patients 50 (53%) received appropriate empirical therapy, whilst for 38 (40%), the therapy was found to be inappropriate. The appropriateness of empirical therapy to 7 (7%) patients could not be determined as the antibiotics prescribed (levofloxacin and cefixime/azithromycin) were not in the AST panel (Figure 3).

# Discussion

This study determined the proportion of microbiologically confirmed UTI cases amongst 552 symptomatic patients and evaluated the appropriateness of empiric antibiotic therapy prescribed to symptomatic UTI patients. Our findings suggest that in about 40% of the cases, empirical antimicrobial prescribing for UTI proves inappropriate in the context of subsequent urine culture and susceptibility results. IEAT can be associated with significant adverse outcomes. Whilst changing to the right antibiotic upon receipt of the culture results is beneficial and necessary for targeted therapy, it may not fully mitigate the disadvantages of not having the correct antibiotic from the onset.<sup>23</sup> IEAT may promote selection pressures that can result in the growth of resistant bacterial populations, which not only affects the individual

I pathogei
5
isolated
of
profiles
AMR
ň
Table

S

	No of organisms toctod						AN	4R, n (%) <sup>~</sup>						
	ווט. טו טוקעוואווא ובאנכע ח <sup>מ</sup>	AMP	AMC	CAZ	CRO	FEP	FOX	GEN	CIP	SXT	NIT	CXM	ERY	LNZ
E. coli	64	53 (83)	30 (47)	29 (45)	33 (52)	29 (45)	8 (12)	15 (22)	39 (61)	49 (77)	3 (5)	58 (91)	N/A	N/A
Klebsiella spp.	21	20 (95)	13 (62)	13 (62)	14 (67)	14 (67)	6 (29)	7 (33)	19 (91)	14 (67)	10 (48)	19 (91)	N/A	N/A
Proteus spp.	7	4 (57)	4 (57)	0	0	0	0	1 (14)	2 (29)	4 (57)	7 (100)	3 (43)	N/A	N/A
P. aeruginosa	2	2 (100)	2 (100)	1 (50)	1 (50)	0	2 (100)	0	0	2 (100)	2 (100)	2 (100)	N/A	N/A
C. koseri	2	1 (50)	0	0	1 (50)	0	0	0	0	0	1 (50)	1 (50)	N/A	N/A
A. baumannii	1	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	N/A	N/A
S. aureus	14	12 (86)	4 (29)	N/A	N/A	N/A	3 (21)	3 (21)	8 (57)	11 (79)	1 (7)	N/A	8 (57)	0
CoNS	7	7 (100)	3 (43)	N/A	N/A	N/A	3 (43)	1 (14)	5 (71)	1 (14)	1 (14)	N/A	55 (71)	0
E. faecalis	6	0	0	N/A	N/A	N/A	6 (100)	6 (100)	5 (83)	2 (33)	1 (17)	N/A	6 (100)	0

 $^{b}n$  (%), frequency of resistant isolates in relation to n expressed in percentage for individual antibiotics; antibiotics not tested in the isolates. <sup>a</sup>n, number of isolates within a particular species.

prim; NIT, nitrofurantoin; CXM, cefuroxime; ERY, erythromycin; LNZ, linezolid; CoNS, coagulase-negative staphylococci; N/A, not applicable.

Furthermore, IEAT can result in unnecessary healthcare costs including expenses associated with additional tests and treatment for complications.<sup>24</sup> These consequences underscore the importance of judicious antibiotic prescribing to optimize patient outcomes and preserve the effectiveness of antibiotics for future generations. It is challenging to find comparable studies because of the wide variation in the way that IEAT is defined. Nevertheless, a recent study by Maina *et al.*<sup>25</sup> investigated the appropriateness of antibiotic use across a range of disease conditions amongst 1502 patients in Kenyan public hospitals. Amongst other findings, these results showed that 26% of 94 patients who had UTI and 68% of 135 patients in the surgical unit received empirical treat-

wide variation in the way that IEAT is defined. Nevertheless, a recent study by Maina *et al.*<sup>25</sup> investigated the appropriateness of antibiotic use across a range of disease conditions amongst 1502 patients in Kenyan public hospitals. Amongst other findings, these results showed that 26% of 94 patients who had UTI and 68% of 135 patients in the surgical unit received empirical treatment that was inappropriate for the pathogens isolated. Higher rates ranging from 54% to 87% of IEAT in UTI have been reported by other studies.<sup>26–30</sup> However, whilst our study defined inappropriate treatment according to the criteria outlined by Davey *et al.*,<sup>23</sup> these studies had a combination of definitions which included antibiotic prescriptions without bacteriological confirmation, prescription of an antibiotic to which isolated pathogen was resistant, inappropriate antibiotic dosage, lack of sensitivity testing and therapy not being within the treatment guidelines.

patient but also poses a broader public health threat to everyone.

Overall, only 1 in 5 patients suspected of having UTI had bacteriological confirmation by the criteria applied in this study (monoculture growth of  $10^4$  cfu/mL). However, a considerable proportion of the patients, 168 (30%), had taken antibiotics prior to the initial hospital visit. This highlights the challenge of conducting and interpreting microbiology culture results in patients previously exposed to antibiotics, as prior research has demonstrated that antibiotic exposure is a strong predictor of negative culture outcomes.<sup>31</sup> This further illustrates the difficulty healthcare providers face in deciding on the need for antibiotic prescriptions based solely on clinical symptoms. Evidence on how well symptoms predict the true presence of UTI when compared with urine culture has shown varied results and is estimated to have an error rate of up to 33%.<sup>31</sup> In this study, 11% of patients had laboratory confirmation of UTIs, yet they did not receive empirical treatment. These findings are comparable with those reported by Alkhawaldeh et al.<sup>26</sup> and Zhu et al.<sup>29</sup>, in which 15.7% and 12.5% patients, respectively, did not receive empirical treatment but were confirmed to have UTI by the culture method. Whilst treating only after the microbiological results are obtained ensures that the correct antimicrobial therapy is chosen, the strategy increases the risk of a worse outcome. These findings highlight the need of a near point-of-care test that can detect UTI and provide preliminary antimicrobial susceptibility reports to guide decision-making in UTI management.

There was a wide variation of empirical antimicrobial prescribing practice amongst prescribers, with differences in preference for certain antimicrobials seen. This was most striking in relation to the prescription of fluoroquinolones (ciprofloxacin and levofloxacin),  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations (AMC) and nitrofurantoin. Despite being a second-line therapy, more than half 140 (51%) of the patients received fluoroquinolones. This is high considering the already reported high resistance<sup>32</sup> and adverse ecological effects<sup>33</sup> associated with this class of antimicrobials. A further 6.3% of the patients received sulfamethoxazole/trimethoprim despite this antibiotic not being amongst



Figure 2. An overview of empirical antimicrobial prescribing at the outpatient departments of MLKH and MCH, Nairobi County, Kenya.

the recommended empirical treatments<sup>16</sup> and local resistance patterns already exceeding 20%.<sup>32</sup> One possible explanation to these findings is the absence of sufficient laboratory support, which influences prescription pattern and choice, leading to a predominance of broad-spectrum prescriptions and polypharmacy.<sup>34</sup> The high-grade resistance exhibited against amoxicillin-clavulanic acid makes this agent suboptimal for UTI treatment in the absence of laboratory support, notwithstanding that it is recommended in the national guidelines as first-line empirical therapy. This illustrates a clear need for more comprehensive national surveillance and perhaps a review of the guidelines. In contrast, nitrofurantoin was an appropriate agent for both Gram-positive and Gram-negative bacteria, and its empirical use is encouraged in the absence of any contraindication.<sup>35</sup>

The high proportion of resistance amongst UTI pathogens reported in this study and in neighbouring countries<sup>17,36</sup> can likely be explained by records of inappropriate antibiotic use which is one of the key drivers of AMR. This could be caused by inadequate microbiology diagnostics, lack of updated antibiotic susceptibility data and self-treatment using over-the-counter antibiotics, a widespread practice in many LMICs.<sup>37</sup> Some challenges identified in laboratory diagnostics have been the long TAT, high cost of investigation and lack of trust in and utilization of laboratory results by clinicians.<sup>38</sup> Performing culture and susceptibility tests may contribute to higher healthcare costs for patients. However, it is essential to consider this added expense in light of the potential savings from avoiding inappropriate or unnecessary treatment that are not supported by laboratory data.

This study has some limitations. First, the patients were only recruited from the outpatient departments of two health facilities, so generalization of findings to other settings, even within Kenva, should be made with caution. Nevertheless, patients were sequentially recruited without stringent selection criteria and the same approach was taken to investigation of every participant which minimized bias and increased the likelihood that the results reflected the general population and routine medical practices. Further, the findings do not give insights into the appropriateness of prescription in private health facilities or in inpatients. However, it is considered satisfactory to provide background information on appropriateness of empirical treatment. Secondly, the population of outpatients who presented with symptoms suggestive of UTI may have had other underlying conditions given that UTI symptoms may overlap with those of other diseases. However, we assumed that all antibiotics prescribed during initial hospital visit before the AST results (when each patient was recruited into the study and urine collected) were for the UTI episode.



**Figure 3.** Evaluation of appropriateness of empirical therapy. Appropriateness or inappropriateness was expressed as a percentage based on *n*=95 patients who had laboratory-confirmed UTI and had susceptible or resistant AST results, respectively.

#### Conclusion

The study has demonstrated that achieving appropriate empirical antibiotic treatment for UTIs is a difficult task, especially in the era of increased AMR in clinical infections, situations of limited resource and much habitual over-the-counter antibiotic use. At present, optimal empiric therapy is not being achieved. This situation could be improved if capacity for delivering accurate and timely susceptibility results to clinicians to aid their clinical decision-making could be achieved. Finally, it is crucial to enhance routine AMR surveillance to support effective antimicrobial stewardship practices in healthcare facilities.

# Acknowledgements

The authors would like to thank all patients for their participation and the laboratory and clinical teams at MLKH, MDH and KEMRI-CMR for their support during the study period.

# Funding

This work was supported by the Scottish Funding Council (SFC) through the Global Challenges Research Fund (GCRF).

# **Transparency declarations**

None to declare.

# Author contributions

H.A.O.: conceptualization, laboratory investigations, data curation, formal analysis and original drafting of the manuscript. R.H.: conceptualization, supervision, reviewing and editing. D.J.S.: conceptualization, supervision, reviewing and editing. M.K.: conceptualization, supervision, reviewing and editing. K.K.: conceptualization, supervision, reviewing and editing. C.N.: supervision of laboratory data collection in Kenya. H.G.: laboratory investigations and data curation

# References

**1** Harbottle H, Thakur S, Zhao S *et al.* Genetics of antimicrobial resistance. *Anim Biotechnol* 2006; **17**: 111–24. https://doi.org/10.1080/10495390 600957092

**2** World Health Organization. *Global Antimicrobial Resistance and Use Surveillance System 2022.* https://www.who.int/publications/i/item/ 9789240062702

**3** O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. The Review on Antimicrobial Resistance, 2014. https://wellcomecollection.org/works/rdpck35v.

**4** Murray CJ, Ikuta KS, Sharara F *et al.* Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022; **399**: 629–55. https://doi.org/10.1016/S0140-6736(21)02724-0

**5** Petti CA, Polage CR, Quinn TC *et al.* Laboratory medicine in Africa: a barrier to effective health care. *Clin Infect Dis* 2006; **42**: 377–82. https://doi. org/10.1086/499363

**6** Elbireer AM, Jackson JB, Sendagire H *et al.* The good, the bad, and the unknown: quality of clinical laboratories in Kampala,

Uganda. *PLoS One* 2013; **8**: e64661. https://doi.org/10.1371/journal.pone. 0064661

**7** Asiimwe BB, Kiiru J, Mshana SE *et al.* Protocol for an interdisciplinary cross-sectional study investigating the social, biological and community-level drivers of antimicrobial resistance (AMR): Holistic Approach to Unravel Antibacterial Resistance in East Africa (HATUA). *BMJ Open* 2021; **11**: 414–18. https://doi.org/10.1136/bmjopen-2020-041418

**8** Ndaki PM, Mushi MF, Mwanga JR *et al.* Dispensing antibiotics without prescription at community pharmacies and accredited drug dispensing outlets in Tanzania: a cross-sectional study. *Antibiotics (Basel)* 2021; **10**: 1025. https://doi.org/10.3390/antibiotics10081025

**9** Green DL, Keenan K, Fredricks KJ *et al.* The role of multidimensional poverty in antibiotic misuse: a mixed-methods study of self-medication and non-adherence in Kenya, Tanzania, and Uganda. *Lancet Glob Heal* 2023; **11**: 59–68. https://doi.org/10.1016/S2214-109X(22)00423-5

**10** Doron S, Davidson LE. Antimicrobial stewardship. *Mayo Clin Proc* 2011; **86**: 1113–23. https://doi.org/10.4065/mcp.2011.0358

**11** Morgan MG, McKenzie H. Controversies in the laboratory diagnosis of community-acquired urinary tract infection. *Eur J Clin Microbiol Infect Dis* 1993; **12**: 491–504. https://doi.org/10.1007/BF01970954

**12** Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf* 2014; **5**: 229–41. https://doi.org/10.1177/20420986145 54919

**13** McCowan C, Bakhshi A, McConnachie A *et al. E. coli* bacteraemia and antimicrobial resistance following antimicrobial prescribing for urinary tract infection in the community. *BMC Infect Dis* 2022; **22**: 805. https://doi.org/10.1186/s12879-022-07768-7

**14** Mazzariol A, Bazaj A, Cornaglia G. Multi-drug-resistant Gram-negative bacteria causing urinary tract infections: a review. *J Chemother* 2017; **29**: 2–9. 10.1080/1120009X.2017.1380395

**15** Gupta K, Hooton TM, Naber KG *et al.* International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011; **52**: e103–20. https://doi.org/10.1093/cid/ciq257

**16** KNH. Kenyatta National Hospital-Guidelines for Empiric Antimicrobial Therapy 2023. https://healthsciences.uonbi.ac.ke/sites/default/files/2023-06/KNH%20Empiric%20Antimicrobial%20Therapy%20Guidelines.pdf

**17** Maldonado-Barragán AA, Mshana SE, Keenan K *et al.* Predominance of multidrug-resistant (MDR) bacteria causing urinary tract infections (UTIs) among symptomatic patients in East Africa: a call for action. *JAC-Antimicrobial Resist* 2024; **6**: dlae019. https://doi.org/10.1093/jacamr/dlae019

**18** Iskandar K, Molinier L, Hallit S *et al.* Surveillance of antimicrobial resistance in low- and middle-income countries: a scattered picture. *Antimicrob Resist Infect Control* 2021; **10**: 63–82. https://doi.org/10. 1186/s13756-021-00931-w

**19** Miles AA, Misra SS, Irwin JO. The estimation of the bactericidal power of the blood. *J Hyg (Lond).* 1938; **38**: 732–49. https://doi.org/10.1017/s002217240001158x

**20** Chesbrough M. *District Laboratory Practice in Tropical Countries, Part 2,* 2nd edn. Cambridge University Press, 2006.

**21** Bauer AW, Kirby WM, Sherris JC *et al.* Antibiotic susceptibility testing by a standardized single disk method. *Am J Clin Pathol* 1966; **45**: 493–6. https://doi.org/10.1093/ajcp/45.4\_ts.493

**22** CLSI. Performance Standards for Antimicrobial Disk Suspectibility Tests, Approved Standard—Thirteenth Edition: M02. 2018.

**23** Davey PG, Marwick C. Appropriate vs. inappropriate antimicrobial therapy. *Clin Microbiol Infect* 2008; **14**: 15–21. https://doi.org/10.1111/j.1469-0691.2008.01959.x

**24** Esparcia A, Artero A, Eiros JM *et al.* Influence of inadequate antimicrobial therapy on prognosis in elderly patients with severe urinary tract infections. *Eur J Intern Med* 2014; **25**: 523–7. https://doi.org/10.1016/j.ejim. 2014.04.009

**25** Maina M, Mwaniki P, Odira E *et al.* Antibiotic use in Kenyan public hospitals: prevalence, appropriateness and link to guideline availability. *Int J Infect Dis* 2020; **99**: 10–8. https://doi.org/10.1016/j.ijid.2020.07.084

**26** Alkhawaldeh R, Farha RA, Hammour KA *et al.* The appropriateness of empiric treatment of urinary tract infections in a tertiary teaching hospital in Joran: a cross-sectional study. *Antibiotics (Basel)* 2022; **11**: 629. https://doi.org/10.3390/antibiotics11050629

**27** Vellinga A, Cormican M, Hanahoe B *et al*. Antimicrobial management and appropriateness of treatment of urinary tract infection in general practice in Ireland. *BMC Fam Pract* 2011; **12**: 108. https://doi.org/10. 1186/1471-2296-12-108

**28** Tünger Ö, Dinç G, Özbakkaloglu B *et al.* Evaluation of rational antibiotic use. *Int J Antimicrob Agents* 2000; **15**: 131–5. https://doi.org/10.1016/S0924-8579(00)00158-8

**29** Zhu H, Chen Y, Hang Y *et al.* Impact of inappropriate empirical antibiotic treatment on clinical outcomes of urinary tract infections caused by *Escherichia coli*: a retrospective cohort study. *J Glob Antimicrob Resist* 2021; **26**: 148–53. https://doi.org/10.1016/j.jgar.2021.05.016

**30** Marquet K, Liesenborgs A, Bergs J *et al*. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. *Crit Care* 2015; **19**: 63. https://doi.org/10. 1186/s13054-015-0795-y

**31** Schmiemann G, Kniehl E, Gebhardt K et al. The diagnosis of urinary tract infection. *Dtsch Ärzteblatt Int* 2010; **107**: 361–7. https://doi.org/10. 3238/arztebl.2010.0361

**32** Kiiru S, Maina J, Katana J *et al.* Bacterial etiology of urinary tract infections in patients treated at Kenyan health facilities and their resistance towards commonly used antibiotics. *PLoS One* 2023; **18**: 277–9. https://doi.org/10.1371/journal.pone.0277279

**33** Stahlmann R, Lode HM. Risks associated with the therapeutic use of fluoroquinolones. *Expert Opin Drug Saf* 2013; **12**: 497–505. https://doi. org/10.1517/14740338.2013.796362

**34** Chokshi A, Sifri Z, Cennimo D *et al.* Global contributors to antibiotic resistance. *J Glob Infect Dis* 2019; **11**: 36–42. https://doi.org/10.4103/jgid.jgid\_110\_18

**35** Pouwels KB, Freeman R, Muller-Pebody B *et al.* Association between use of different antibiotics and trimethoprim resistance: going beyond the obvious crude association. *J Antimicrob Chemother* 2018; **73**: 1700–7. https://doi.org/10.1093/jac/dky031

**36** Silago V, Moremi N, Mtebe M *et al.* Multidrug-resistant uropathogens causing community acquired urinary tract infections among patients attending health facilities in Mwanza and Dar es Salaam, Tanzania. *Antibiotics (Basel)* 2022; **11**: 1718. https://doi.org/10.3390/antibiotics11121718

**37** Do NTT, Vu HTL, Nguyen CTK *et al.* Community-based antibiotic access and use in six low-income and middle-income countries: a mixed-method approach. *Lancet Glob Heal* 2021; **9**: e610–9. https://doi.org/10. 1016/S2214-109X(21)00024-3

**38** Alemnji GA, Zeh C, Yao K *et al*. Strengthening national health laboratories in sub-Saharan Africa: a decade of remarkable progress. *Trop Med Int Heal* 2014; **19**: 450–8. https://doi.org/10.1111/tmi.12269